2. THE SCIENTIFIC ABSTRACT

This Phase I (pilot) open-label human gene therapy protocol tests the safety and feasibility of using autologous T cell clones that have been genetically modified to be specific for CD19 and expanded *ex vivo*, in five patients between the ages of 16 and 75 with high risk follicular lymphoma (Fl) of B cell origin. The autologous T cells are rendered specific for CD19 by electroporating with a naked DNA plasmid construct coding for a chimeric immunoreceptor and a bifunctional fusion gene that combines hygromycin phosphotransferase and herpes virus thymidine kinase (HyTK) permitting *in vitro* selection with hygromycin and potential *in vivo* ablation of transferred cells with ganciclovir. The specificity of the scFvFc:ζ chimeric immunoreceptor is derived from the variable regions of a mouse mAb specific for CD19 that are tethered to the T cell via the human IgG4 Fc region and CD4 transmembrane domain. Upon binding CD19, the genetically modified T cells are activated by the cytoplasmic CD3-ζ chain attached to the chimeric immunoreceptor. Genetically modified T cells are selected for growth in hygromycin, cloned by limiting dilution, evaluated for specific lysis of $CD19^+$ targets and expanded to large numbers in compliance with current Good Manufacturing Practice (GMP). Prior to adoptive immunotherapy research participants will have recovered from prior therapy. Research participants will receive Rituximab to reduce the number of circulating normal and malignant B cells prior to adoptive immunotherapy. The first T cell dose to be given on day 0 is at $1x10^8/m^2$. Fludarabine will be given on day 7 and 8 to help eradicate and prevent a host immune response directed against the genetically modified T cells. Approximately, six days after the last dose of fludarabine, a series of four intra-patient escalating T cell infusions typically given over four weeks will be administered with the same autologous genetically modified cytolytic clone beginning at $2x10^9$ cells/m^2 and cumulating at $4x10^9$ cells/m^2. Self-administered subcutaneous low-dose recombinant human IL-2 may be used to support the *in vivo* persistence of the T cells after T cell doses #2, #3, #4 and #5. The study will continue to accrue until at least 5 research participants have received at least two infusions of genetically modified T cells. These research participants will be evaluated for safety and persistence of the infused T cells, safety of using exogenous IL-2, generation of an immune response by the recipient against the infused genetically modified T cells and anti-tumor responses. It is likely that additional studies will be necessary to establish the ability of the CD19-specific T cells to eradicate Fl.